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(71) Applicants (*for all designated States except US*):
SOCRATECH L.L.C. [US/US]; 3643 Lenawee Avenue,
Los Angeles, CA 90016 (US). THE UNIVERSITY OF
ROCHESTER [US/US]; 518 Hylan Building, Rochester,
NY 14627 (US).

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(72) Inventors; and

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(75) Inventors/Applicants (*for US only*): ZLOKOVIC,
Berislav, V. [US/US]; 3345 Elmwood Avenue, Rochester,
NY 14610 (US). WU, Zhenhua [CN/US]; 14 Tabor Place,
Apt. #2, Brookline, MA 02445 (US). DEANE, Rashid
[GB/US]; 2 Argyle Street, Rochester, NY 14607 (US).

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(74) Agent: TANIGAWA, Gary, R.; Nixon & Vanderhye P.C.,
901 North Glebe Road, 11th Floor, Arlington, VA 22203-
1808 (US).

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(54) Title: ROLE OF GAX IN ALZHEIMER NEUROVASCULAR DYSFUNCTION

(57) Abstract: Neurovascular disorder critically contributes to the development and pathogenesis of Alzheimer's disease (AD). Transcriptional profiling of human brain endothelial cells (BEC) defines a subset of age-independent genes significantly altered in AD including the homeobox gene *GAX* whose expression controls vascular phenotype and is low in AD. By using viral-mediated *GAX* gene silencing and transfer, restoring *GAX* expression in AD BEC is angiogenic, transcriptionally suppresses the AFX1 forkhead transcription factor-mediated apoptosis, and increases the levels of a major amyloid β -peptide ($\text{A}\beta$) clearance receptor, the low density lipoprotein receptor-related protein 1 (LRP-1) at the blood-brain barrier. In a mouse model of Alzheimer's disease, deletion of the *Gax* gene results in reductions in brain capillary density and the resting cerebral blood flow, loss of angiogenic brain response to hypoxia, and an impaired $\text{A}\beta$ brain efflux caused by reduced LRP-1 levels. The link of *GAX* gene to AD neurovascular dysfunction provides new mechanistic and therapeutic insights into AD.

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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

IPC: A01N 43/04(2006.01);C12N 15/00(2006.01),15/63(2006.01);C07H 21/02(2006.01),21/04(2006.01)

USPC: 514/44;435/320.1,455;536/23.1,23.5,24.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/44; 435/320.1, 455; 536/23.1, 23.5, 24.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
WEST, STN, MEDLINE, CAPLUS, BIOSIS, SCISEARCH, LIFESCI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A — X	MAILLARD et al., Percutaneous Delivery of the Gax gene Inhibits Vessel Stenosis in a Rabbit Model of Balloon Angioplasty, Cardiovascular Research, 1997, Vol. 35, pages 536-346, especially abstract.	1-19 ----- 20
A	PERLMAN et al., Adenovirus-Mediated Delivery of the Gax Transcription Factor to Rat Carotid Arteries Inhibits Smooth Muscle Proliferation and Induces Apoptosis, Gene Therapy, 1999, Vol. 6, pages 758-763, especially abstract.	1-20

Further documents are listed in the continuation of Box C.

See patent family annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
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Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	Authorized officer Shin-Lin Chen <i>Felicia D. Roberts</i> Telephone No. 703-308-0196 <i>fdr</i>

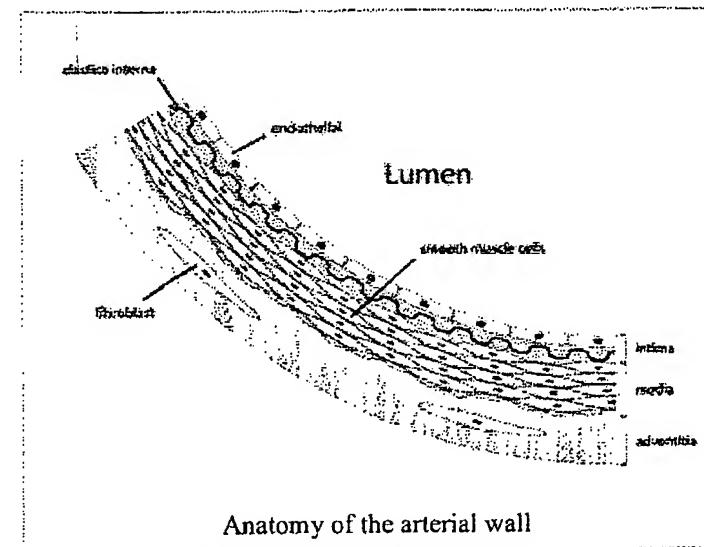
Endothelium

From Wikipedia, the free encyclopedia

The **endothelium** is the thin layer of cells that line the interior surface of blood vessels, forming an interface between circulating blood in the lumen and the rest of the vessel wall. Endothelial cells line the entire circulatory system, from the heart to the smallest capillary. These cells reduce friction of the flow of blood allowing the fluid to be pumped further.

Endothelial tissue is a specialized type of epithelium tissue (one of the four types of biological tissue in animals). More specifically, it is simple squamous epithelium.

Endothelium of the interior surfaces of the heart chambers are called endocardium. Both blood and lymphatic capillaries are composed of a single layer of endothelial cells.



Anatomy of the arterial wall

Contents

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Function

Endothelial cells are involved in many aspects of vascular biology, including:

- vasoconstriction and vasodilation, and hence the control of blood pressure
- blood clotting (thrombosis & fibrinolysis)
- atherosclerosis
- formation of new blood vessels (angiogenesis)
- inflammation and swelling (oedema)

Endothelial cells also control the passage of materials — and the transit of white blood cells — into and out of the bloodstream.

In some organs, there are highly differentiated endothelial cells to perform specialized 'filtering' functions. Examples of such unique endothelial structures include the renal glomerulus and the blood-

brain barrier.

Pathology

Endothelial dysfunction, or the loss of proper endothelial function, is a hallmark for vascular diseases, and often leads to atherosclerosis. This is very common in patients with diabetes mellitus, hypertension or other chronic pathophysiological conditions. One of the main mechanisms of endothelial dysfunction is the diminishing of nitric oxide, often due to high levels of asymmetric dimethylarginine, which interfere with the normal L-arginine-stimulated nitric oxide synthesis.

See also

- Endothelium-derived relaxing factor (EDRF)
- Robert F. Furchtgott (1998 Nobel prize for discovery of EDRF)
- Caveolae
- Weibel-Palade bodies
- Endothelial microparticles
- Endothelial progenitor cells
- Endocardium
- Tunica intima
- Apelin

External links

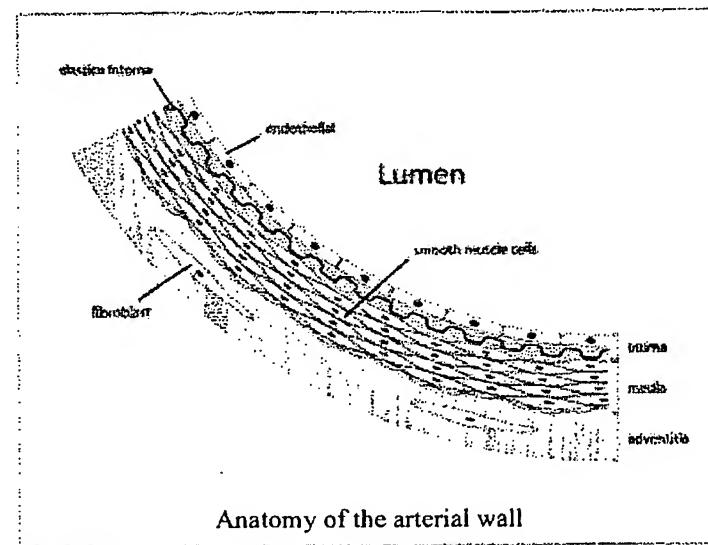
- *endothelium* (<http://www.emedicine.com/asp/dictionary.asp?keyword=endothelium>) at eMedicine Dictionary
- Organology at UC Davis *Circulatory/vessels/capillaries1/capillaries3* (<http://trc.ucdavis.edu/mjguinan/apc100/modules/Circulatory/vessels/capillaries1/capillaries3.htm>)
- "Capillaries, non-fenestrated (EM, Low)"
- Histology at BU *214020oa* (<http://www.bu.edu/histology/p/214020oa.htm>)

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["http://en.wikipedia.org/wiki/Endothelium"](http://en.wikipedia.org/wiki/Endothelium)

Categories: Cardiovascular system | Tissues



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